inhibitory drugs other than celecoxib and are not therefore limited to the preferred embodiment for which patent rights are sought in the present application.

Claims 26 and 60 are cancelled as they embrace a process or composition having a broader range of celecoxib amount than is present in the preferred embodiment for which patent rights are sought in the present application.

Claims 8, 27, 58 and 61 are cancelled as, following amendment herein of Claims 1 and 42 from which they depend, they do not further limit the scope of Claims 1 and 42.

Claim 1 is amended to require that the selective COX-2 inhibitory drug used in the claimed process is celecoxib in an amount of about 15% to about 75% by weight. Claim 42 is amended to require that the selective COX-2 inhibitory drug in the claimed composition is celecoxib and is present in an amount of about 15% to about 75% by weight. Support for these amendments can be found in Claims 8, 27, 58 and 61 as filed. Support for celecoxib as a preferred selective COX-2 inhibitor can also be found throughout the specification, for example at page 11, line 22 and in Examples 1 and 2 (pages 31–34). Support for the range of about 15% to about 75% celecoxib can be found in the specification at least at page 22, lines 22–25.

Claim 42 is further amended by insertion of the word "uniformly" before "dispersed". The term "dispersed" already implies absence of large insoluble aggregates of celecoxib; however, addition of "uniformly" clarifies that this is what is intended. That uniformity of dispersion in the matrix is an important feature of the invention is supported in the specification at least at page 5, lines 18–19.

Claims 14, 15, 28, 29, 62 and 63 are amended to recite celecoxib as the specific selective COX-2 inhibitory drug, to ensure proper antecedent basis for these claims.

No new matter is introduced by the present amendment, and no change in inventorship results therefrom.

RESPONSE TO OFFICE ACTION DATED SEPTEMBER 27, 2002

1. Information Disclosure Statement

Applicant mailed the required copies of documents cited in the Information Disclosure Statement (IDS) dated June 27, 2002, together with that IDS and Form PTO-1449, and can only assume that the large volume of documents became detached from the IDS and Form PTO-1449 during handling in the Patent and Trademark Office. Enclosed herewith for the Examiner's convenience is a further copy of each of the cited documents. This completes the

IDS of June 27, 2002. No further fee is believed payable in connection with this IDS; however, if it should be determined that a fee is required, please charge such fee to Deposit Account No. 19-1025.

2. Double Patenting

Certain claims in the present application stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Serial No. 09/932,500.

As this is a provisional rejection, a Terminal Disclaimer is not being filed at this time; furthermore, with amendment herein to limit the present claims by recitation of celecoxib as the selective COX-2 inhibitor, Applicant respectfully submits that the double patenting rejection is overcome without need for a Terminal Disclaimer.

The Examiner has requested a copy of the claims of five copending applications that she indicates "appear to be directed towards the same subject matter" as the present application. Copies are enclosed herewith. Applicant notes that of the five applications listed, only two, Serial No. 09/932,500 and Serial No. 09/932,537, are drawn to oral fast-melt tablet formulations. It is further noted that one of the applications referenced, Serial No. 09/731,350, is abandoned.

3. Rejections under 35 U.S.C. § 103

Claims 1–3, 10–25, 28–53, 62–83 and 86–89 are pending in the present Application following amendment herein.

3.1. Rejection over Mizumoto and Nakao

Claims 1–3, 10–16, 18–21, 23–25, 28–44, 46–49, 51–53, 62–83 and 86–89 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mizumoto (U.S. Patent No. 5,576,014) and Nakao (U.S. Patent No. 6,277,878). This rejection is respectfully traversed.

Mizumoto represents "state of the art" formulation technology useful for preparing an oral fast-melt tablet at the time of the present invention, as will be clear from the context in which the Mizumoto reference is cited in the present specification (paragraph bridging pages 4 and 5). However, when applying this technology to a poorly soluble selective COX-2 inhibitory drug, in particular to celecoxib, certain challenges arise. In this regard, the Examiner's attention is respectfully directed to the present specification, which states at page 5, lines 11–19:

> "Celecoxib also presents difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties. Due at least in part to these properties, celecoxib crystals tend to segregate and agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. Therefore, it is difficult to prepare a fast-melt composition containing celecoxib that has the desired blend uniformity for rapid and complete disintegration in the mouth."

Applicant respectfully submits that the Examiner has overlooked the problem faced by the present inventors and the solution to that problem embodied in the invention, namely incorporation in the process of "means to inhibit agglomeration of the drug" as recited in Claim 1 as filed. By amendment herein to provide celecoxib as the drug in question, the inventiveness of the process as defined in Claim 1 should be more instantly clear. "Means to inhibit agglomeration" can be any such means, as set forth in the specification at page 8, lines 8–22, illustratively including addition of a wetting agent, pre-wetting the powder to be granulated, and/or increasing air flow around the granulation vessel.

The Examiner admits that Mizumoto does not specifically teach the active agent formulated according to Mizumoto's claimed process to be a selective COX-2 inhibitor. Claim 1 of the present application as filed requires the active agent to be a selective COX-2 inhibitor; further, Claim 1 has now been amended to recite a specific selective COX-2 inhibitor, namely celecoxib. In light of the Examiner's admission, in combination with the present amendment, the invention as now claimed is nonobvious in view of Mizumoto.

Nakao does not disclose celecoxib among the selective COX-2 inhibitory drugs listed therein, and provides no teaching or suggestion relevant to the preparation of an oral fast-melt formulation, thus fails to contemplate the problem faced by the present inventors and to propose a solution. Nakao does not disclose, explicitly or inherently, incorporation in any formulation process of means to inhibit agglomeration of a drug that is prone to segregation and agglomeration.

Thus, Nakao does not teach or suggest celecoxib nor does Nakao teach or suggest means to inhibit agglomeration. Therefore one of skill in the art, faced with the problem of formulating celecoxib, a drug having a tendency to agglomerate, would not have been motivated to modify the teaching of Mizumoto in view of Nakao. Furthermore, even if he had

modified the teaching of Mizumoto in view of Nakao, he would not have arrived at the present invention.

The combination of Mizumoto and Nakao, even if these references are combinable (which is not admitted herein), fails to teach or suggest all limitations of Claim 1 as amended herein. Specifically, the combination is silent as to celecoxib and as to means to inhibit agglomeration of the celecoxib. Furthermore, the combination is silent as to uniformity of dispersion of celecoxib in a matrix, as recited in Claim 42 as amended herein. No *prima facie* case of obviousness can therefore be sustained (M.P.E.P. § 2143.03). Withdrawal of the rejection of all claims rejected under 35 U.S.C. § 103(a) as unpatentable over Mizumoto and Nakao is therefore respectfully requested.

3.2. Rejection over Mizumoto and Nakao in view of Talley '272 and Talley '068

All claims rejected under 35 U.S.C. § 103(a) as being unpatentable over Mizumoto and Nakao in view of Talley (U.S. Patent No. 5,633,272) and Talley (U.S. Patent No. 5,760,068) are cancelled by the present amendment. However, as the subject matter of original Claims 8 and 58, specifying celecoxib as the selective COX-2 inhibitory drug, is incorporated in Claims 1 and 42 respectively as amended herein, Applicant considers the present rejection as applicable to these claims and all claims dependent therefrom. This rejection is respectfully traversed.

Talley '272 relates to valdecoxib, not celecoxib and is not relevant to the present claims.

Talley '068 discloses celecoxib. The Examiner states that "it would have been obvious for the skilled artisan to, by routine experimentation, modify the anti-inflammatory agent of Mizumoto and Nakao using ... celecoxib in view of the teachings of Talley". Even if this statement is true, which is not admitted herein, such modification would not have led to the present invention.

As discussed above, celecoxib presents difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties, as well as having a relatively high dose requirement. It was the present inventors' discovery that an acceptable formulation could be made by incorporating means to inhibit agglomeration, a critical process limitation not taught or suggested by the combination of Mizumoto, Nakao and Talley.

By failure to teach or suggest all limitations of Claims 1 and 42 as amended herein, the

combination of Mizumoto, Nakao and Talley cannot lead to a conclusion of *prima facie* obviousness of these claims or any claim dependent therefrom (M.P.E.P. § 2143.03). Withdrawal of the rejection of all claims rejected under 35 U.S.C. § 103(a) as unpatentable over Mizumoto and Nakao in view of Talley '272 and Talley '068 is therefore respectfully requested.

3.3. Rejection over Mizumoto and Nakao in view of Jain

Claims 17, 22, 45 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mizumoto and Nakao in view of Jain (U.S. Patent No. 6,316,029). This rejection is respectfully traversed.

It is first noted that Claims 17 and 22 depend from independent Claim 1 and that Claims 45 and 50 depend from independent Claim 42, thus these dependent claims incorporate all limitations present in the corresponding independent claims. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. M.P.E.P. § 2143.03, first paragraph; *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

The Examiner has not rejected Claims 1 and 42 under 35 U.S.C. § 103 except over Mizumoto and Nakao. Jain fails to add the two elements of Claim 1 missing from the combination of Mizumoto and Nakao, namely celecoxib and means to inhibit agglomeration. Thus although Jain discloses sodium lauryl sulfate and silicon dioxide, the combination of Mizumoto and Nakao in view of Jain (even if these references are combinable, which is not admitted) fails to teach or suggest all limitations of Claims 17 and 22. Similarly, Jain fails to add two elements of Claim 42 missing from the combination of Mizumoto and Nakao, namely celecoxib and uniform dispersion thereof. Thus although Jain discloses sodium lauryl sulfate and silicon dioxide, the combination of Mizumoto and Nakao in view of Jain (even if these references are combinable, which is not admitted) fails to teach or suggest all limitations of Claims 45 and 50.

Sodium lauryl sulfate is disclosed in the present specification as an illustrative wetting agent that can act as a means to inhibit agglomeration and assist in providing a uniform dispersion of celecoxib. Even if the disclosure of sodium lauryl sulfate in Jain is considered to amount to inherent disclosure of means to inhibit agglomeration (which is not admitted herein), Jain still fails to teach or suggest celecoxib. Jain's "Compound A" is said to be a "COX-2 inhibitor type ... NSAID" (Jain, column 12 lines 16–18) but is not disclosed to be a selective COX-2 inhibitor such as celecoxib.

Furthermore, the composition of Example 1 of Jain is said to be prepared by applying 100 g of a liquid dispersion containing 20% Compound A, 4% HPC and 0.12% sodium lauryl sulfate on to 125 g lactose, and then formulating 746 mg of the resulting dried granules (which can be calculated to contain 100 mg Compound A) with other ingredients to provide a tablet of total weight 2000 mg. The amount of Compound A present in the composition is thus about 5% by weight, far below the minimum of about 15% required for celecoxib in the present claims as amended herein. The amount of sodium lauryl sulfate is about 0.03%, a very small amount that is unlikely to give the advantage sought according to the present invention. See the present specification at page 24 lines 27–30:

> "One or more wetting agents, if desired, are present in compositions of the present invention in a total amount of about 0.05% to about 5%, preferably about 0.075% to about 2.5%, and more preferably about 0.25% to about 1%, for example about 0.5%, by weight of the composition."

Thus addition of Jain to the combination of Mizumoto and Nakao already shown above as failing to support a *prima facie* conclusion of obviousness does not lead to a different conclusion. Specifically, the combination of Mizumoto and Nakao in view of Jain fails to teach or suggest all limitations of the present claims and no *prima facie* case of obviousness can therefore be sustained (M.P.E.P. § 2143.03). Withdrawal of the rejection of Claims 17, 22, 45 and 50 under 35 U.S.C. § 103(a) as unpatentable over Mizumoto and Nakao in view of Jain is therefore respectfully requested.

4. Conclusion

All claims presently in consideration are believed now to be in condition for allowance.

Respectfully submitted,

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Enclosures
Amendments in the claims in marked-up form in accordance with 37 C.F.R. § 1.121(c)(1)(ii)
Fee Transmittal Form
Claims of U.S. application Serial No. 09/731,350 as filed
Claims of U.S. application Serial No. 09/874,504 as filed
Claims of U.S. application Serial No. 09/932,500 as filed
Claims of U.S. application Serial No. 09/932,537 as filed
Claims of U.S. application Serial No. 10/113,157 as filed
Further copies of documents cited in IDS of June 27, 2002

MARKED UP VERSION OF AMENDMENTS MADE IN CLAIMS

1. A process for preparing an oral fast-melt pharmaceutical composition, the process comprising

   (a) a step of wet granulating [a selective cyclooxygenase-2 inhibitory drug] celecoxib in an amount of about 15% to about 75% by weight of the composition together with a liquid binding agent comprising a saccharide having high moldability, and

   (b) a step of blending with the [drug] celecoxib a saccharide having low moldability,

   wherein steps (a) and (b) occur in any order or simultaneously to result in formation of granules, and wherein the process incorporates means to inhibit agglomeration of the [drug] celecoxib.

14. The process of Claim 1 wherein said means to inhibit agglomeration comprises pre-wetting the [drug] celecoxib prior to said step (a).

15. The process of Claim 1 wherein said means to inhibit agglomeration of the [drug] celecoxib comprises addition of a wetting agent.

28. The process of Claim 1 wherein [said selective cyclooxygenase-2 inhibitory drug] the celecoxib is present in [a total] an amount of about 30% to about 75% by weight of the composition.

29. The process of Claim 1 wherein [said selective cyclooxygenase-2 inhibitory drug] the celecoxib is present in [a total] an amount of about 45% to about 75% by weight of the composition.

42. An oral fast-melt composition comprising [a selective cyclooxygenase-2 inhibitory drug] celecoxib in an amount of about 15% to about 75% by weight of the composition, uniformly dispersed in a matrix comprising a saccharide of low moldability and a saccharide of high moldability.

62. The composition of Claim 42 wherein the [selective cyclooxygenase-2 inhibitory drug] celecoxib is present in an amount of about 30% to about 75% by weight of the composition.

63. The composition of Claim 42 wherein the [selective cyclooxygenase-2 inhibitory

drug] celecoxib is present in an amount of about 45% to about 75% by weight of the composition.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm.

2. The composition of Claim 1 having total bioavailability that is greater than that of an otherwise similar composition wherein substantially all of the particles are larger than 1 μm.

3. The composition of Claim 1 exhibiting a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm.

4. The composition of Claim 1 wherein substantially all of the particles are smaller than 1 μm.

5. The composition of Claim 1 wherein the dose units are in the form of discrete solid articles.

6. The composition of Claim 5 wherein the solid articles are tablets or capsules.

7. The composition of Claim 1 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.

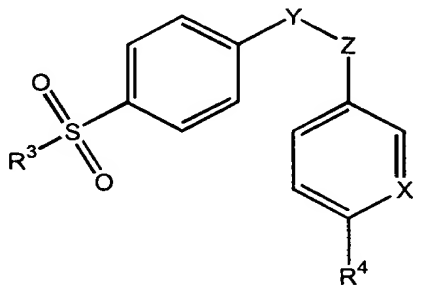
8. The composition of Claim 7 wherein the substantially homogeneous flowable mass is a liquid suspension.

9. The composition of Claim 1 wherein the solid particles have a D_{25} particle size of about 450 nm to about 1000 nm.

10. The composition of Claim 1 wherein about 25% to 100% by weight of the solid particles have a particle size of about 450 nm to about 1000 nm.

11. The composition of Claim 1 wherein the solid particles have a weight average particle size of about 450 nm to about 1000 nm.

12. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

13. The composition of Claim 12 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

14. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

15. The composition of Claim 14 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

16. The composition of Claim 15 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

17. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, and wherein about 25% to 100% by weight of the particles are smaller than 1 μm.

18. The composition of Claim 17 wherein substantially all of the particles are smaller than 1 μm.

19. The composition of Claim 17 wherein the dose units are in the form of discrete solid articles.

20. The composition of Claim 19 wherein the solid articles are tablets or capsules.

21. The composition of Claim 17 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.

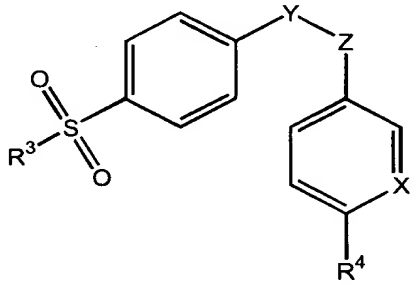
22. The composition of Claim 21 wherein the substantially homogeneous flowable mass is a liquid suspension.

23. The composition of Claim 17 wherein the solid particles have a D_{25} particle size of about 450 nm to about 1000 nm.

24. The composition of Claim 17 wherein about 25% to 100% by weight of the solid particles have a particle size of about 450 nm to about 1000 nm.

25. The composition of Claim 17 wherein the solid particles have a weight average particle size of about 450 nm to about 1000 nm.

26. The composition of Claim 17 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

27. The composition of Claim 26 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

28. The composition of Claim 17 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib,

5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

29. The composition of Claim 28 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

30. The composition of Claim 29 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

31. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering one or more dose units of a composition of Claim 1 one to about six times a day.

32. The method of Claim 31 wherein the medical condition or disorder is accompanied by acute pain.

33. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering one or more dose units of a composition of Claim 17 one to about six times a day.

34. The method of Claim 33 wherein the medical condition or disorder is accompanied by acute pain.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

2. The composition of Claim 1 wherein the second drug is an alkylxanthine compound.

3. The composition of Claim 2 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

4. The composition of Claim 2 wherein the alkylxanthine compound is caffeine.

5. The composition of Claim 1 having total bioavailability of said selective cyclooxygenase-2 inhibitory drug that is greater than that of an otherwise similar composition wherein substantially all of said selective cyclooxygenase-2 inhibitory drug particles are larger than 1 μm.

6. The composition of Claim 1 exhibiting a substantially shorter time to reach a therapeutically effective threshold blood serum concentration of said selective cyclooxygenase-2 inhibitory drug, by comparison with an otherwise similar composition wherein substantially all of the selective cyclooxygenase-2 inhibitory drug particles are larger than 1 μm.

7. The composition of Claim 1 wherein substantially all of said selective cyclooxygenase-2 inhibitory drug particles are smaller than 1 μm.

8. The composition of Claim 1 wherein the dose units are in the form of discrete solid articles.

9. The composition of Claim 8 wherein the solid articles are tablets or capsules.

10. The composition of Claim 1 that is in the form of a substantially homogeneous flowable

mass from which single dose units are measurably removable.

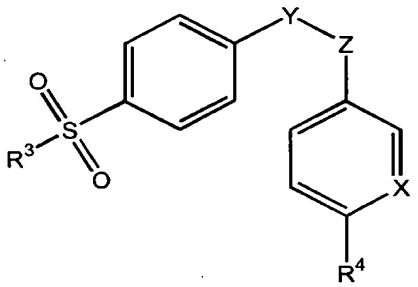
11. The composition of Claim 10 wherein the substantially homogeneous flowable mass is a liquid suspension.

12. The composition of Claim 1 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a D_{25} particle size of about 450 nm to about 1000 nm.

13. The composition of Claim 1 wherein about 25% to 100% by weight of said solid selective cyclooxygenase-2 inhibitory drug particles have a particle size of about 450 nm to about 1000 nm.

14. The composition of Claim 1 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a weight average particle size of about 450 nm to about 1000 nm.

15. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

16. The composition of Claim 15 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

17. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

18. The composition of Claim 17 wherein the selective cyclooxygenase-2 inhibitory drug is

celecoxib.

19. The composition of Claim 18 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

20. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

21. The method of Claim 20 wherein the second composition comprises an alkylxanthine compound.

22. The method of Claim 21 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

23. The method of Claim 21 wherein the alkylxanthine compound is caffeine.

24. The method of Claim 20 wherein the subject suffers from headache or migraine and wherein the first and second compositions are administered in total and relative amounts effective to relieve pain in the headache or migraine.

25. The method of Claim 20 wherein the first and second compositions are administered at substantially the same time.

26. The method of Claim 20 wherein the first and second compositions are administered at substantially different times.

27. A method of analgesia comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of a composition of Claim 1.

28. The method of Claim 27 wherein the subject suffers from headache or migraine and wherein said composition is administered in an amount effective to relieve pain in the

headache or migraine.

29. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, and wherein about 25% to 100% by weight of the particles are smaller than 1 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

30. The composition of Claim 29 wherein the second drug is an alkylxanthine compound.

31. The composition of Claim 30 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

32. The composition of Claim 30 wherein the alkylxanthine compound is caffeine.

33. The composition of Claim 29 wherein substantially all of said solid selective cyclooxygenase-2 inhibitory drug particles are smaller than 1 μm.

34. The composition of Claim 29 wherein the dose units are in the form of discrete solid articles.

35. The composition of Claim 34 wherein the solid articles are tablets or capsules.

36. The composition of Claim 29 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.

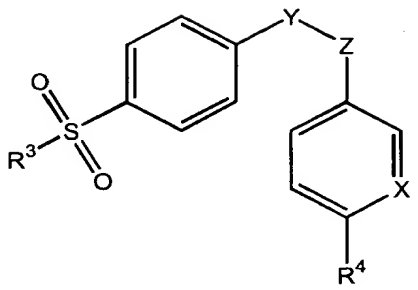
37. The composition of Claim 36 wherein the substantially homogeneous flowable mass is a liquid suspension.

38. The composition of Claim 29 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a D_{25} particle size of about 450 nm to about 1000 nm.

39. The composition of Claim 29 wherein about 25% to 100% by weight of said solid selective cyclooxygenase-2 inhibitory drug particles have a particle size of about 450 nm to about 1000 nm.

40. The composition of Claim 29 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a weight average particle size of about 450 nm to about 1000 nm.

41. The composition of Claim 29 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

42. The composition of Claim 41 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

43. The composition of Claim 29 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

44. The composition of Claim 43 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

45. The composition of Claim 44 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

46. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, wherein about 25% to 100% by weight of the particles are smaller than 1 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

47. The method of Claim 46 wherein the second composition comprises an alkylxanthine compound.

48. The method of Claim 47 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

49. The method of Claim 47 wherein the alkylxanthine compound is caffeine.

50. The method of Claim 46 wherein the subject suffers from headache or migraine and wherein the first and second compositions are administered in total and relative amounts effective to relieve pain in the headache or migraine.

51. The method of Claim 46 wherein the first and second compositions are administered at substantially the same time.

52. The method of Claim 46 wherein the first and second compositions are administered at substantially different times.

53. A method of analgesia comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of a composition of Claim 29.

54. The method of Claim 53 wherein the subject suffers from headache or migraine and wherein said composition is administered in an amount effective to relieve pain in the headache or migraine.

55. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition in which at least 80% of the drug by weight is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

56. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) nanoparticles of a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in nanoparticle form in an amount to

provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition containing the same amount of drug as is present in the nanoparticles wherein at least 80% of the drug by weight in the otherwise similar composition is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

57. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition in which at least 80% of the drug by weight is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

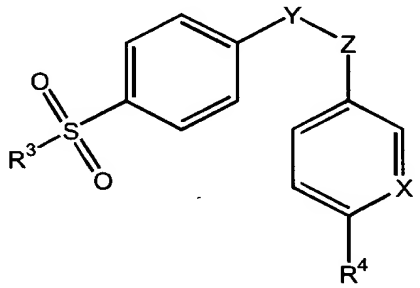
58. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising nanoparticles of a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in nanoparticle form in an amount to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition containing the same amount of drug as is present in the nanoparticles wherein at least 80% of the drug by weight in the otherwise similar composition is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

WHAT IS CLAIMED IS:

1. A process for preparing an oral fast-melt pharmaceutical composition, the process comprising (a) a step of wet granulating a selective cyclooxygenase-2 inhibitory drug together with a binding agent selected from gums, polypeptides, natural and modified starches, cellulosic materials, alginic acid and salts thereof, polyethylene glycol, polyvinylpyrrolidone, polymethacrylates, silicate salts and bentonites; and (b) a step of blending with the drug a saccharide having low moldability, wherein said steps (a) and (b) occur in any order or simultaneously to result in formation of granules.

2. The process of Claim 1 wherein said step (b) occurs prior to or simultaneously with said step (a).

3. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is a compound having the formula:



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups; or a prodrug of such a compound.

4. The process of Claim 3 wherein the five-to six-membered ring is selected from cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

5. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

6. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is

selected from celecoxib, valdecoxib, rofecoxib and etoricoxib.

7. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

8. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is valdecoxib.

9. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in an amount of about 0.1% to about 60% by weight of the composition.

10. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 4% to about 60% by weight of the composition.

11. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 10% to about 60% by weight of the composition.

12. The process of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 20% to about 60% by weight of the composition.

13. The process of Claim 1 wherein said saccharide having low moldability is selected from lactose, mannitol, glucose, sucrose and xylitol.

14. The process of Claim 1 wherein said saccharide having low moldability is mannitol of powder grade.

15. The process of Claim 1 wherein said saccharide having low moldability is present in an amount of about 10% to about 90% by weight of the composition.

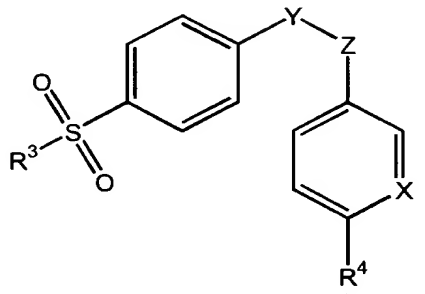
16. The process of Claim 1, further comprising (c) a step of blending said granules with at least one of a lubricant, a sweetening agent and a flavoring agent to form a tableting blend; and (d) a step of compressing the tableting blend to form oral fast-melt tablets.

17. The process of Claim 16 wherein parameters are set in said compressing step (d) to provide tablets having a hardness of about 1 to about 10 kp.

18. An oral fast-melt pharmaceutical composition prepared by the process of Claim 1.

19. An oral fast-melt composition comprising a selective cyclooxygenase-2 inhibitory drug dispersed in a matrix comprising a saccharide of low moldability and a binding agent selected from gums, polypeptides, natural and modified starches, cellulosic materials, alginic acid and salts thereof, polyethylene glycol, polyvinylpyrrolidone, polymethacrylates, silicate salts and bentonites.

20. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is a compound having the formula:



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups; or a prodrug of such a compound.

21. The composition of Claim 20 wherein the five-to six-membered ring is selected from cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

22. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

23. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, rofecoxib and etoricoxib.

24. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

25. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is valdecoxib.

26. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is present in an amount of about 0.1% to about 60% by weight of the composition.

27. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 4% to about 60% by weight of the composition.

28. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 10% to about 60% by weight of the composition.

29. The composition of Claim 19 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 20% to about 60% by weight of the composition.

30. The composition of Claim 19 wherein said saccharide having low moldability is selected from lactose, mannitol, glucose, sucrose and xylitol.

31. The composition of Claim 19 wherein said saccharide having low moldability is mannitol of powder grade.

32. The composition of Claim 19 wherein said saccharide having low moldability is present in an amount of about 10% to about 90% by weight of the composition.

33. The composition of Claim 19 that is a tablet.

34. The tablet of Claim 33 that disintegrates within about 30 to about 300 seconds in a standard *in vitro* disintegration assay.

35. The tablet of Claim 33 that disintegrates within about 5 to about 60 seconds after placement in the oral cavity of a subject.

36. A method of treating a medical condition or disorder in a mammalian subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of Claim 19.

37. The method of Claim 36 wherein said mammalian subject is a human subject.

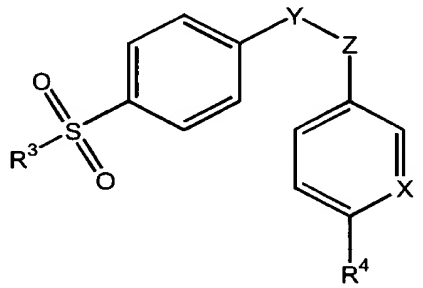
38. The method of Claim 37 that further comprises combination therapy with one or more drugs selected from opioids and other analgesics.

39. The method of Claim 37 that further comprises combination therapy with an opioid compound selected from codeine, meperidine, morphine and derivatives thereof.

WHAT IS CLAIMED IS:

1. A molded article for administration to an oral cavity of a subject to treat or prevent a cyclooxygenase-2 mediated condition, disorder or disease, the molded article comprising a moldable blend of a therapeutically effective amount of a selective cyclooxygenase-2 inhibitory drug with a pharmaceutically acceptable excipient carrier system consisting predominantly of one or more carbohydrates, wherein ingredients and amounts thereof in the molded article and a process for preparing the molded article are selected such that the molded article exhibits rapid disintegration in the oral cavity, and wherein the moldable blend is prepared by a process step not requiring wet granulation.

2. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is a compound having the formula:



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups; or a prodrug of such a compound.

3. The molded article of Claim 2 wherein the five-to six-membered ring is selected from cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

4. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

5. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, rofecoxib and etoricoxib.

6. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

7. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is valdecoxib.

8. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in an amount of about 0.1% to about 60% by weight of the molded article.

9. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 4% to about 60% by weight of the molded article.

10. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 10% to about 60% by weight of the molded article.

11. The molded article of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 20% to about 60% by weight of the molded article.

12. The molded article of Claim 1 wherein the carbohydrate(s) present in the excipient carrier system are selected from natural and modified celluloses, natural and modified starches, mono-, di- and oligosaccharide sugars and sugar alcohols.

13. The molded article of Claim 1 wherein at least one carbohydrate present in the excipient carrier system is a sugar or sugar alcohol.

14. The molded article of Claim 13 wherein the sugar or sugar alcohol is selected from erythritol, glucose, lactose, maltitol, maltose, mannitol, sorbitol, sucrose and xylitol.

15. The molded article of Claim 13 wherein the sugar or sugar alcohol is one that exhibits rapid dissolution in the mouth.

16. The molded article of Claim 13 wherein the sugar or sugar alcohol is one that exhibits rapid dissolution in the oral cavity of a subject and provides a sweet taste.

17. The molded article of Claim 1 wherein one or more carbohydrates are present in a total amount of about 20% to about 90% by weight of the molded article.

18. The molded article of Claim 1 that is a wafer, a lozenge or a tablet.

19. The molded article of Claim 1 that is an oral fast-melt tablet.

20. The tablet of Claim 19 that disintegrates within about 5 to about 60 seconds after placement in the oral cavity of a subject.

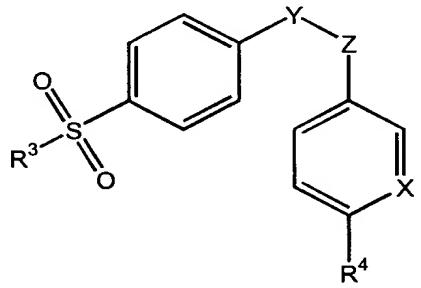
21. The tablet of Claim 19 having a hardness of about 1 to about 10 kp.

22. The tablet of Claim 19 having sufficient hardness to resist breakage of the tablet during removal from standard blister packaging by pushing the tablet through a cover sheet.

23. The tablet of Claim 19 having sufficient hardness to enable tablets to be packaged together in a glass or plastic bottle, without individual packaging, whereby the tablets do not exhibit substantial breakage or sticking and/or melding together during normal shipping and handling.

24. A process for preparing a molded article suitable as an oral fast-melt dosage form of a selective cyclooxygenase-2 inhibitory drug, the process comprising a step of intimately mixing the drug in a therapeutically effective amount with an excipient carrier system predominantly consisting of one or more carbohydrates, to form a blend, wherein formation of the blend does not require wet granulation; and a step of shaping a unit-dose quantity of the blend in a mold to form the molded article.

25. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is a compound having the formula:



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups; or a prodrug of such a compound.

26. The process of Claim 25 wherein the five-to six-membered ring is selected from cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

27. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-

(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

28. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, valdecoxib, rofecoxib and etoricoxib.

29. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

30. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is valdecoxib.

31. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is present in an amount of about 0.1% to about 60% by weight of the molded article.

32. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 4% to about 60% by weight of the molded article.

33. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 10% to about 60% by weight of the molded article.

34. The process of Claim 24 wherein the selective cyclooxygenase-2 inhibitory drug is present in a total amount of about 20% to about 60% by weight of the molded article.

35. The process of Claim 24 wherein the carbohydrate(s) present in the excipient carrier system are selected from natural and modified celluloses, natural and modified starches, mono-, di- and oligosaccharide sugars and sugar alcohols.

36. The process of Claim 24 wherein at least one carbohydrate present in the excipient carrier system is a sugar or sugar alcohol.

37. The process of Claim 36 wherein the sugar or sugar alcohol is selected from erythritol, glucose, lactose, maltitol, maltose, mannitol, sorbitol, sucrose and xylitol.

38. The process of Claim 36 wherein the sugar or sugar alcohol is one that exhibits rapid dissolution in the mouth.

39. The process of Claim 36 wherein the sugar or sugar alcohol is one that exhibits rapid dissolution in the oral cavity of a subject and provides a sweet taste.

40. The process of Claim 24 wherein one or more carbohydrates are present in a total amount of about 20% to about 90% by weight of the molded article.

41. The process of Claim 24 wherein the shaping step comprises direct compression of the blend to form a tablet.

42. The process of Claim 24 further comprising a step of removing a solvent from the molded article by freeze-drying, vacuum-drying or lyophilization.

43. The process of Claim 24 wherein the excipient carrier system is prepared as a shearform matrix to which the drug is added, and wherein the shaping step comprises compression of the shearform matrix.

44. A molded article prepared by the process of Claim 24.

45. A method of treating a medical condition or disorder in a mammalian subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a molded article of Claim 1.

46. The method of Claim 45 wherein said mammalian subject is a human subject.

47. The method of Claim 45 that further comprises combination therapy with one or more drugs selected from opioids and other analgesics.

48. The method of Claim 45 that further comprises combination therapy with an opioid compound selected from codeine, meperidine, morphine and derivatives thereof.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

2. The composition of claim 1 wherein the second drug is an alkylxanthine compound.

3. The composition of claim 2 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

4. The composition of claim 2 wherein the alkylxanthine compound is caffeine.

5. The composition of claim 1 having total bioavailability of said selective cyclooxygenase-2 inhibitory drug that is greater than that of an otherwise similar composition wherein substantially all of said selective cyclooxygenase-2 inhibitory drug particles are larger than 1 μm.

6. The composition of claim 1 exhibiting a substantially shorter time to reach a therapeutically effective threshold blood serum concentration of said selective cyclooxygenase-2 inhibitory drug, by comparison with an otherwise similar composition wherein substantially all of the selective cyclooxygenase-2 inhibitory drug particles are larger than 1 μm.

7. The composition of claim 1 wherein substantially all of said selective cyclooxygenase-2 inhibitory drug particles are smaller than 1 μm.

8. The composition of claim 1 wherein the dose units are in the form of discrete solid articles.

9. The composition of claim 8 wherein the solid articles are tablets or capsules.

10. The composition of claim 1 that is in the form of a substantially homogeneous flowable

mass from which single dose units are measurably removable.

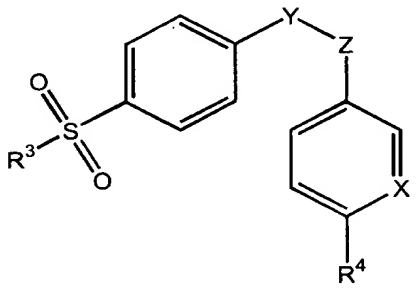
11. The composition of claim 10 wherein the substantially homogeneous flowable mass is a liquid suspension.

12. The composition of claim 1 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a D_{25} particle size of about 450 nm to about 1000 nm.

13. The composition of claim 1 wherein about 25% to 100% by weight of said solid selective cyclooxygenase-2 inhibitory drug particles have a particle size of about 450 nm to about 1000 nm.

14. The composition of claim 1 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a weight average particle size of about 450 nm to about 1000 nm.

15. The composition of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

16. The composition of Claim 15 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

17. The composition of claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

18. The composition of claim 17 wherein the selective cyclooxygenase-2 inhibitory drug is

celecoxib.

19. The composition of claim 18 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

20. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

21. The method of claim 20 wherein the second composition comprises an alkylxanthine compound.

22. The method of claim 21 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

23. The method of claim 21 wherein the alkylxanthine compound is caffeine.

24. The method of claim 20 wherein the subject suffers from headache or migraine and wherein the first and second compositions are administered in total and relative amounts effective to relieve pain in the headache or migraine.

25. The method of claim 20 wherein the first and second compositions are administered at substantially the same time.

26. The method of claim 20 wherein the first and second compositions are administered at substantially different times.

27. A method of analgesia comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of a composition of claim 1.

28. The method of claim 27 wherein the subject suffers from headache or migraine and wherein said composition is administered in an amount effective to relieve pain in the

headache or migraine.

29. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, and wherein about 25% to 100% by weight of the particles are smaller than 1 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

30. The composition of claim 29 wherein the second drug is an alkylxanthine compound.

31. The composition of claim 30 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

32. The composition of claim 30 wherein the alkylxanthine compound is caffeine.

33. The composition of claim 29 wherein substantially all of said solid selective cyclooxygenase-2 inhibitory drug particles are smaller than 1 μm.

34. The composition of claim 29 wherein the dose units are in the form of discrete solid articles.

35. The composition of claim 34 wherein the solid articles are tablets or capsules.

36. The composition of claim 29 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.

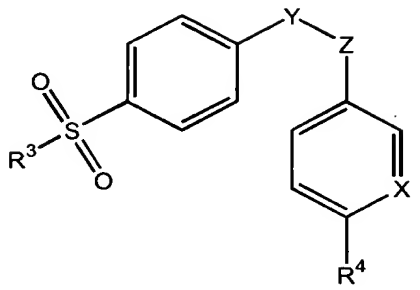
37. The composition of claim 36 wherein the substantially homogeneous flowable mass is a liquid suspension.

38. The composition of claim 29 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a D_{25} particle size of about 450 nm to about 1000 nm.

39. The composition of claim 29 wherein about 25% to 100% by weight of said solid selective cyclooxygenase-2 inhibitory drug particles have a particle size of about 450 nm to about 1000 nm.

40. The composition of claim 29 wherein said solid selective cyclooxygenase-2 inhibitory drug particles have a weight average particle size of about 450 nm to about 1000 nm.

41. The composition of Claim 29 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

42. The composition of claim 41 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

43. The composition of claim 29 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

44. The composition of claim 43 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

45. The composition of claim 44 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

46. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, wherein about 25% to 100% by weight of the particles are smaller than 1 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

47. The method of claim 46 wherein the second composition comprises an alkylxanthine compound.

48. The method of claim 47 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

49. The method of claim 47 wherein the alkylxanthine compound is caffeine.

50. The method of claim 46 wherein the subject suffers from headache or migraine and wherein the first and second compositions are administered in total and relative amounts effective to relieve pain in the headache or migraine.

51. The method of claim 46 wherein the first and second compositions are administered at substantially the same time.

52. The method of claim 46 wherein the first and second compositions are administered at substantially different times.

53. A method of analgesia comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of a composition of claim 29.

54. The method of claim 53 wherein the subject suffers from headache or migraine and wherein said composition is administered in an amount effective to relieve pain in the headache or migraine.

55. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition in which at least 80% of the drug by weight is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

56. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising (a) nanoparticles of a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in nanoparticle form in an amount to

provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition containing the same amount of drug as is present in the nanoparticles wherein at least 80% of the drug by weight in the otherwise similar composition is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second drug selected from vasomodulators and alkylxanthine compounds; wherein the selective cyclooxygenase-2 inhibitory drug and the second drug are present in total and relative amounts effective to relieve pain.

57. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition in which at least 80% of the drug by weight is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.

58. A method of analgesia comprising orally administering, to a subject in need of analgesia, (a) a first pharmaceutical composition comprising one or more orally deliverable dose units, each comprising nanoparticles of a selective cyclooxygenase-2 inhibitory drug of low water solubility wherein the drug is present in nanoparticle form in an amount to provide a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter time to reach a threshold blood serum concentration for therapeutic effect, by comparison with an otherwise similar composition containing the same amount of drug as is present in the nanoparticles wherein at least 80% of the drug by weight in the otherwise similar composition is in the form of particles larger than 1 μm and smaller than 10 μm, and (b) a second pharmaceutical composition comprising a vasomodulator and/or an alkylxanthine compound; wherein the first and second compositions are administered in total and relative amounts effective to relieve pain.